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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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John P. White
Cooper & Dunham LLP
1185 Avenue Of the Americas
New York, NY 10036

EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,682	FEINSTEIN ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7 and 9-29* is/are pending in the application.

4a) Of the above claim(s) *10-23 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,9,24 and 26-29* is/are rejected.

7)☒ Claim(s) *7 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *01/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Preliminary Amendment filed June 4, 2001, the Amendment filed August 1, 2002, and the Amendment filed December 2, 2002 have been entered. The paper and computer readable forms of the Sequence Listing filed August 1, 2002 have also been entered.

Election/Restriction

2. Applicant's election with traverse of Group I, and of SEQ ID NOS 56, 57, and 41, in the Communications filed December 2, 2002 and March 24, 2003 is acknowledged.

In the Communication filed December 2, 2002, applicant argues that while the examiner has indicated that "in claims 1-9, 20 and 24, methods of detecting nucleic acids and polypeptides and methods of treating employing nucleic acids and polypeptides are improperly joined," the claims in fact "deal only with polynucleotides and not with polypeptides," and that "The term 'polypeptide-encoding polynucleotide' refers to polynucleotides only." This argument has been thoroughly considered but is not found persuasive. It is acknowledged that the term "polypeptide-encoding polynucleotide" refers to polynucleotides only. However, the claims as written encompass both polynucleotides and polypeptides. For example, claim 6 requires that "the analyzing step include the step of using a specific antibody to detect the presence of a polypeptide encoded by said polynucleotide." Such language clearly indicates that the claims encompass polypeptide detection. Regarding claim 20, the claim recites a compound "which inhibits a gene, or polypeptide encoded thereby." Accordingly, applicant's arguments are not persuasive.

In the Communication filed March 24, 2003, applicant argues that the examiner's requirement to elect particular SEQ ID Nos is improper because a search of all SEQ ID Nos would not be a serious burden. The response argues that "a search of the prior art relevant to any of the SEQ ID NOS. would necessarily turn up the prior art relevant to the claims of the SEQ ID NOS., and *vice versa* because all of the SEQ ID NOS. are detected in the claimed method for diagnosing bladder cancer." This argument has been thoroughly considered but is not found persuasive. As was previously indicated by the examiner, each of the SEQ ID Nos encompassed by the claims has a different structure and function. A search of all of the sequences recited in the claims would require not only a separate sequence database search for each sequence, but separate text search queries for each of the different genes/proteins corresponding to the recited SEQ ID Nos. As the claims as written encompass numerous different combinations of particular molecules, examination would further require review and consideration of all the prior art related to each individual combination encompassed by the claims. As a different field of search would be required for each of the combinations encompassed by the claims, examination of the multitude of combinations encompassed by the claims would pose a serious burden on the examiner (see *MPEP* 803 and 808.02). Accordingly, applicant's arguments are not persuasive.

The requirement is still deemed proper and is therefore made **FINAL**.

3. Claims 10-23 and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement

in the Communication of December 2, 2002. Further, with regard to elected claims 1-2, 4-7, 9, 24 and 26-29, combinations of SEQ ID NOS 42, 45, 61, 48, 51, 47, 55, 58, 43, 44, 53, 49, 60, 59, 52, 46 and 50 are withdrawn from consideration as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Communication of March 24, 2003.

Claims 1-2, 4-7, 9, 24 and 26-29, as limited to the combination of SEQ ID NOS 56 and 57, as well as the combination of SEQ ID NOS 56, 57, and 41, are now under consideration.

Priority

4. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. In the instant case, applicant's priority claim is improper because it does not identify the relationship (continuation, continuation-in-part, etc.) between the instant application and PCT/US00/41005. Correction is required.

Information Disclosure Statement

5. In a "Communication" filed March 25, 2003, applicant provided a copy of a 1449 filed in application no. 09/670,672, and requested that the Communication and '672

1449 be "placed in the file" of the instant application. It is noted that applicant did not provide copies of the listed references, and did not request that a copy of the '672 1449 be signed/initialed by the examiner. The examiner has reviewed the '672 application, including the references present in that file. However, the 1449 copy provided in the instant application does not properly identify each of the cited documents. Specifically, 37 CFR 1.98(b) requires that U.S. Patents be identified by inventor, patent number, and issue date; that foreign patents be identified by country, document number, and publication date; and that other publications be identified by publisher, author (if any), title, relevant pages, date, and place of publication. Further, it is not clear from applicant's Communication as to whether applicant wishes for the examiner to acknowledge consideration of the cited references by providing a signed/initialed copy of the '672 1449 in the instant application. As applicant has not requested that the examiner sign/initial the '672 1449, and as the majority of the citations provided thereon are incomplete, a signed/initialed copy has not been provided with the instant Office action. **However, if applicant wishes for the references cited on the '672 1449 to be listed on any patent issuing from the instant application, a signed/initialed 1449 will be required. Accordingly, if applicant wishes for the references cited on the '672 1449 to be printed, applicant should provide, in response to this Office action, a 1449 that includes complete citations for each of the references.** Applicant is not required to provide copies of U.S. Patents or of any references that were provided in the '672 application, as those references are available to the examiner.

It is also noted that a subset of the references cited on the '672 1449 were cited separately by applicant in the instant application on a 1449 filed January 14, 2003, and that a signed and initialed copy of that 1449 is enclosed herewith.

Specification

6. The title of the invention is not descriptive of the subject matter of the elected claims. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Methods of diagnosing bladder cancer.

7. The use of the trademark TAQMAN® has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Objections

8. Claims 7 and 9 are objected to because of the following informalities: claim 7 recites "stageTa" rather than "stage Ta" and claim 9 recites "stageT1" rather than "stage T1." Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-2, 4-7, 9, 24, and 26-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of diagnosing bladder cancer/bladder TCC in which increased expression of SEQ ID Nos 56 and 57, alone or in combination with SEQ ID NO: 41, is detected as indicative of said cancer, does not reasonably provide enablement for methods in which increased expression of these molecules is detected as an indicator of stage Ta and/or stage T1 of bladder cancer/TCC or any other type of TCC, or as an indicator of the presence of TCC other than bladder TCC, or for methods of diagnosing cancer in non-human patients. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

The claims are drawn to methods of diagnosing bladder cancer (claims 1-2, 4-6, 24, and 26-29), and methods of diagnosing stage Ta (claim 7) and stage T1 (claim 9) of

transitional cell carcinoma ("TCC"). The claims require detection of the level of expression of at least two polynucleotides in a patient sample, wherein a higher level of expression as compared to a sample from a cancer free subject is indicative of bladder cancer (claims 1-2, 4-6, 24, 26-29), stage Ta of TCC (claim 7), or stage T1 of TCC (claim 9). It is noted that dependent claims 26-27 require the detection of three polynucleotides. It is also noted that the elected invention requires determining the expression of SEQ ID Nos 56-57, or (for those claims requiring determination of three polynucleotides), SEQ ID Nos 56-57 in combination with SEQ ID NO: 41. The specification teaches that SEQ ID NOS 56 and 57 correspond to known genes encoding hepatocyte growth factor activator inhibitor type 2 and syndecan-1, respectively, while SEQ ID NO: 41 is not homologous to any known gene (see, e.g., Table 5).

It is unpredictable as to whether one of skill in the art could make and use applicant's invention in a manner reasonably commensurate with the instant claims. The specification teaches that the genes corresponding to SEQ ID NOS 56, 57 and 41 "were found to be upregulated in at least 60% of TCC samples and unchanged in at least 75% of the normal samples" (p. 40), and provide evidence that SEQ ID Nos 56, 57, and 41 are upregulated in many bladder TCC samples as compared to healthy controls (see Tables 1 and 2). Accordingly, the teachings of the specification indicate that the levels of expression of SEQ ID NOS 56, 57 and 41 are frequently elevated in bladder TCC tissues, and thus increased expression of these genes/molecules is one factor that one of skill in the art would reasonably consider in diagnosing bladder cancer/bladder TCC. Regarding determining stages Ta and/or T1 of TCC, the

specification teaches that "Keratin 13 is identified herein as a marker that can differentiate Ta from T1 and invasive tumors" (page 47), and provides evidence that keratin 13 is "upregulated in Ta tumors and downregulated in T1 tumors when compared to normal urothelium" (page 47; see also pages 72-73). However, none of the elected sequences corresponds to keratin 13, and the specification does not provide evidence that detection of levels of SEQ ID Nos 56 and 57, alone or in combination with SEQ ID NO 41, allows one to actually determine the stage of TCC present. Rather, while the data presented in Tables 1 and 2 provides evidence of increased expression of these molecules in bladder TCC as compared to normal samples, levels detected among stage Ta and T1 samples appear to be variable and overlapping, and the specification does not otherwise provide evidence that, e.g., particular levels of expression correlate with stage Ta and/or stage T1. Further, the evidence provided in the specification is limited to data obtained with human bladder TCC samples (as compared to normal human tissues). The specification does not provide evidence of an association between expression levels of SEQ ID NOS 56/57/41 and other types of TCC (i.e., non bladder TCC), or of an association between expression of any of these polynucleotides and cancer of any type in non-human patients.

Lacking guidance from the specification, one of skill in the art may look to the teachings of the prior art for further clarification and enablement of a claimed invention. The prior art as exemplified by Orntoft (U.S. 6,335,170 B1 [1/2002; filed 2/2000]) discloses that the genes encoding syndecan-1 and hepatocyte growth factor activator inhibitor type 2 were assayed for differential expression in bladder tumors, and were not

among those that were found to be differentially expressed in Orntoft's assays (see entire reference, particularly Figure 6). Both Jalkanen et al (U.S. 5,422,243 A [6/1995]) and Rintala et al (Gynecologic Oncology 75:372-378 [12/1999]) provide evidence that syndecan-1 expression is decreased in tumor cells as compared to healthy cells in some types of tumors (in Jalkanen et al, see entire reference, particularly, e.g., col 3, line 67-col 4, line 25; in Rintala et al, see entire reference, particularly page 376). Rintala et al also disclose that expression levels of syndecan-1 are not associated with cervical carcinoma stage (see entire reference, particularly page 376). Accordingly, in the instant case, the prior art does not provide evidence of an association between expression levels of SEQ ID NOS 56/57/41 and bladder TCC stage, or with respect to any association between increased expression of these polynucleotides and other types of TCC. Further, the prior art is silent with respect to any correlation between these particular polynucleotides and cancers in non-human patients. Thus, given the lack of guidance provided by the specification and the art, it is unpredictable as to whether one of skill in the art could make and use applicant's invention in a manner reasonably commensurate with the claims. While it is clearly within the ability of one of skill in the art to conduct further experimentation to determine whether such associations exist, the outcome of such research cannot be predicted, and therefore it is unpredictable as to whether any quantity of experimentation would be sufficient to enable applicant's invention as now claimed. While one of skill in the art could clearly practice methods of diagnosing bladder cancer/bladder TCC in which increased expression of SEQ ID Nos 56 and 57, alone or in combination with SEQ ID NO: 41, it would require undue

experimentation to make and use applicant's invention in a manner reasonably commensurate with the instant claims.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-2, 4-7, 9, 24, and 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2, 4-7, 9, 24, and 26-29 are indefinite over the recitation of the language "the polynucleotides having sequences represented by...." It is first noted that independent claims 1, 7, and 9 do not previously refer to "polynucleotides having sequences represented by...," and therefore do not provide antecedent basis for this language. It is unclear as to what particular polynucleotides would be considered to constitute "the polynucleotides having sequences represented by" the particular SEQ ID Nos recited in the claims, and as to how such molecules might differ from "polynucleotides having sequences represented by..." Clarification is required.

Claim 5 is indefinite over the recitation of the limitations "the analyzing step" and "the step of using RT-PCR technology," because there is insufficient antecedent basis for these limitations in the claims.

Claim 6 is indefinite over the recitation of the limitations "the analyzing step" and "the step of using a specific antibody...," because there is insufficient antecedent basis for these limitations in the claims.

Claim 6 is indefinite because it is unclear as to how the claim is intended to further limit claim 1, from which it depends. The claim is drawn to a method "according to claim 1, wherein the analyzing step includes the step of using a specific antibody to detect the presence of a polypeptide encoded by said polynucleotide." It is again noted that there is insufficient antecedent basis for the recitation "the analyzing step;" claim 1 does not include such a step. It is unclear as to whether the instant claim is intended to require detection of a polypeptide as an indicator of polynucleotide levels (i.e., such that direct detection of polynucleotide is not required), or whether this language is intended to require a step to be performed in addition to polynucleotide detection. Accordingly, the metes and bounds of the claim are unclear.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
June 12, 2003